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Laxatives: Clinical Pharmacology and Rational Use

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Summary

Proprietary laxatives represent a multimillion dollar industry and are widely used by the apparently well population. They are traditionally classified into bulk laxatives, lubricants, stimulants, stool softeners, and osmotic laxatives. The latter 3 probably act mainly by favouring accumulation of fluids and electrolytes in the lumen of the gut. Magnesium-containing saline laxatives are believed to act by releasing cholecystokinin which, in turn, favours intraluminal fluid accumulation. Bran is not a proprietary laxative. It is a bulking agent with capacity to hold water in the stool, thereby improving bowel function. The lubricant, mineral oil (liquid paraffin), is obsolete.

In constipation associated with the spastic colon, bran will transform the difficult-to-pass scybala into softer, bulkier and more easily passed stools. Atonic constipation, in which defaecation fails to be triggered by a full rectum, is less satisfactorily treated with bran. In these individuals, chronic laxative use often compounds the problem. Bowel retraining with occasional (and decreasing) use of laxatives such as bisacodyl or 'Senokot' (standardised senna) are often effective. Occasionally, a glycerin suppository will trigger the defaecation reflex.

Patients with an acute illness, undergoing surgery or suffering from perianal disease benefit from the early institution of bran to encourage the easy passage of soft stool. Bisacodyl or 'Senokot' should be kept in reserve. In patients who become impacted, particularly following a barium enema, an oil retention enema followed by a tap water enema may be successful, but manual disimpaction should not be unduly delayed. Laxatives may alter the appearance of the colon mucosa and so should be avoided before sigmoidoscopy. Preparation for an air contrast barium enema or colonoscopy necessitates a 2 day program of laxation including a fluid diet.

Laxatives are probably more important to modern medicine for the harm they do than for their benefit. Use of the stimulant cathartics can lead to an atonic colon in which the neuromuscular apparatus is permanently damaged. Vigorous purgation may produce a paradoxical diarrhoea complicated by electrolyte derangement, malabsorption, and protein-losing enteropathy. Other than bran, most clinicians will have little need for laxatives and their use by patients should also be discouraged.

In 1973 it was estimated that Americans paid $130 million for proprietary laxatives (Binder and Donowitz, 1975). Approximately 22% of apparently healthy Britons use laxatives other than bran and 6% use them at least twice a week (Thompson and Heaton, 1979). Thus, like alcohol and tobacco, laxatives are big business and are probably more important for the harm they do to otherwise healthy people, than for their benefit to mankind. In fact, there is evidence that many laxative consumers can be 'maintained' on placebo (Griener et al., 1957).

This review will examine the classification and clinical pharmacology of some of the available laxatives, and discuss their rational and irrational use.

1. Clinical Pharmacology

Laxatives are traditionally classified as shown in table I. This classification is based on concepts of intestinal activity and does not take into account the effect of laxatives on fluid and electrolyte movements through the gut wall. Binder and Donowitz (1975) have pointed out that many laxatives in the stimulant, stool softener and osmotic groups act by favouring fluid and electrolyte accumulation in the intestinal lumen. Magnesium-containing cathartics appear to act by releasing cholecystokinin. Thus, it has been suggested that a new classification be formulated, taking these mechanisms into account. However, this has not yet been possible and the present discussion will be based on tradition.

Table I. Laxatives in current use

1. Bulk-forming preparations
   a) Bran
   b) Psyllium mucilloid
   c) Ispaghula extract
   d) Sterculia extract
   e) Bassorin derivatives
2. Stimulants
   a) Diphenylmethanes
      i) Phenolphthalein
      ii) Bisacodyl
   b) Anthracene glycosides
      i) Senna
      ii) Cascara
      iii) Danthron
   c) Castor oil
3. 'Stool softeners'
   Dioctyl sodium sulphosuccinate (DSS)
4. Osmotic laxatives
   a) Magnesium salts (magnesium sulphate; magnesium hydroxide; magnesium citrate)
   b) Sodium salts (sodium phosphate-biphosphate)
   c) Lactulose

1.1 Bulk Laxatives

1.1.1 Bran

The laxative effect of bran has been known since the time of Hippocrates. For centuries, man has strived for whiter and whiter bread, and now flour contains very little bran (Thompson, 1979). It is this removal of fibre from the diet that many authors such as Burkitt et al. (1974) and Cleave (1974) believe is responsible for the colon diseases of western man. Indeed, these diseases, particularly constipation, appear to be rare in Africans eating a native diet (Trowell, 1977; Segal and Hunt, 1975).

Whether or not fibre deficiency is responsible for constipation, there is no doubt that bran is effective in preventing it (Streicher and Quirk, 1943). Patients with the spastic, constipated type of irritable bowel notice that larger, softer and more easily passed stools replace hard scybala (Thompson, 1979). Those with an atonic colon and full rectum are less likely to respond.

Bran expands and softens the stool (Cowgill and Anderson, 1932; Williams and Olmsted, 1936), reduces intracolonic pressure (Brodribb et al., 1979) and hastens gastrointestinal transit in constipated individuals (Harvey et al., 1973; Payler et al., 1975). It is believed to achieve these effects because of its water (and gas) holding capacity. For example fine bran

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which holds less water per unit weight has less effect on stool bulk (Brodribb and Groves, 1978). The bulking effect of bran is due largely to its pentose-containing polysaccharides (Cummings et al., 1978). The production of volatile fatty acids by the bacterial degradation of bran in the colon may also be important. These fatty acids may act similarly to ricinoleic acid, the active principle of castor oil, to produce intestinal fluid accumulation (Kerzner et al., 1979).

Burkitt and others have demonstrated that the African stool is 4 times as large and twice as rapidly passed through the gut as its English counterpart (Burkitt et al., 1972). Small stools of western man may not be large enough to stimulate the defaecation reflex. Thus, bran would seem to be the safest, cheapest and most physiological method of treating and preventing chronic constipation.

Wheat bran is contraindicated in obstructive lesions or coeliac disease. In the latter condition, rice bran has been successfully employed.

1.1.2 Psyllium and Other Bulk-forming Preparations

Of the many other bulking agents available, psyllium hydrophilic mucilloid is probably the most commonly used ('Metamucil'; 'Hydrocil'). Dextrose is added as a dispersing agent. The effectiveness of psyllium also appears to depend upon its water-holding capacity (Cass and Wolf, 1952; Belarian et al., 1952; Gray and Tainter, 1941), and it has been found useful in the treatment of both atonic and spastic constipation.

Other bulk-forming preparations available include ispaghula extracts ('Isogel'; 'Fybogel'), sterculia gum extracts ('Normocol') and bassorin derivatives ('Granocol').

1.2 Lubricants

The petroleum product, mineral oil (liquid paraffin) was introduced at the turn of the century and millions of gallons have passed through intestinal pipelines since. It appears to have no pharmacological action on the gut or stool, and acts only by lubricating the passage of recalcitrant scybala.

Chronic use of liquid paraffin may lead to lipoid pneumonia in the elderly (Zurrow and Sergay, 1966; Freiman et al., 1940; Javert and Macri, 1941). Anal incontinence (Jones and Godding, 1972) or pruritus ani may result from leaking oil and it has also been accused of being carcinogenic (Boyd and Doll, 1954). For these reasons it will not be discussed further.

1.3 Stimulants

There are 3 commonly used types of stimulant laxatives: the diphenylmethane laxatives, the anthracene glycosides, and castor oil.

1.3.1 Diphenylmethane Laxatives

Phenolphthalein

Phenolphthalein was originally used to colour wine, with predictable effects on the consumer. It is absorbed from the gut and some is excreted via the kidney (Fantus and Dyniewicz, 1938). The drug also undergoes enterohepatic circulation and is excreted in the bile as phenolphthalein glucuronide in which form it exerts its laxative action (Cumings, 1974). It is, therefore, ineffective in obstructive jaundice (Steigman et al., 1938). In the rat, phenolphthalein appears to act by inhibiting water absorption (Surawicz et al., 1977).

Oxyphenisatin, which is related to phenolphthalein, has been reported to cause chronic active hepatitis (McHardy and Balart, 1970). This drug should no longer be used.

Bisacodyl

Bisacodyl is available as both a suppository and enteric-coated tablet. The latter normally has no action on the small bowel, but if taken with an alkali, the coating may dissolve, causing unpleasant cramps. At first it was believed to act by initiating peristalsis in the colon (Hardcastle and Mann, 1968). However, its laxative effect now seems more likely to be due to

the intraluminal accumulation of water (Ewe et al., 1977). Recent reports suggest that this is accomplished by intestinal inhibition of Na-K-ATPase, stimulation of adenyl cyclase, and an increase in mucosal prostaglandin E_2 (Rachmilewitz and Karmeli, 1979). There is evidence that the drug also undergoes enterohepatic circulation (Cummings et al., 1974), but this does not appear to be important for its efficacy (Thompson, 1979).

1.3.2 Anthracene Glycosides (Senna and Cascara)

Senna and cascara are more potent than phenolphthalein on a molar basis (Hubacher and Doernberg, 1964) and of the two, senna is said to be superior to cascara (Duncan, 1957). These substances undergo a rather unusual metabolism. The intact molecule is ineffective on the colon (Hardcastle and Wilkins, 1970). When administered orally, the glycoside is hydrolysed by colonic bacteria to release glucose and the active principle, an aglycone. This increases peristalsis of the colon and decreases sigmoidal segmentation (Waller, 1975; Fairbairn, 1958). The drugs appear to act on the intramural nerves and plexes of the colon (Douthwaite and Goulding, 1957). Cascara apparently alters electrolyte transport through the gut (Phillips et al., 1965). However it would appear that, like other laxatives, cascara achieves its effect largely through the accumulation of fluids and electrolytes in the gut.

Curiously, the aglycones given orally are not effective. The sugar moeity appears to ensure their survival through the small intestine (Hardcastle and Wilkins, 1970).

1.3.3 Danthron

Unlike senna and cascara, danthron is sugar-free and has a low molecular weight. This allows its absorption by the gut and detoxification by the liver. The urine may also become pink or orange in colour. Nursing mothers using this drug may produce catharsis in their infants. Because it is absorbed, it is less potent and potentially more toxic than the glycosides (Godding, 1976).

1.3.4 Castor Oil

This ancient cathartic is a triglyceride which is hydrolysed in the small intestine by pancreatic enzymes to release glycerol and ricinoleic acid. The latter is the active principle. Its laxative effect depends upon cyclic AMP mediated fluid secretion (Binder et al., 1977) but it also damages the gut epithelium (Cline et al., 1976; Gaginella et al., 1977; Bernier et al., 1979).

Castor oil was used to lubricate aircraft in World War I, but many consider its action too violent for peacetime use.

1.4 'Stool Softeners'

Dioctyl sodium sulphosuccinate (DSS) is an anionic detergent which softens the stool by net water accumulation in the intestine (Donowitz and Binder, 1975). A recent report suggests that this is accomplished by inhibition of Na-K-ATPase, stimulation of adenyl cyclase and a decrease in mucosal prostaglandin E_2 (Rachmilewitz and Karmeli, 1979). It is therefore similar in its action to the stimulant laxative, bisacodyl.

DSS disrupts the colonic epithelium (Bernier et al., 1979) and, like aspirin, disrupts the gastric mucosal barrier (Cochran et al., 1977). It favours the absorption of normally unabsorbed substances such as mineral oil and oxyphenisatin (Naess, 1970). Therefore, it should not be used in combination with certain other drugs.

1.5 Osmotic Laxatives

1.5.1 Magnesium and Sodium Salts

The cations magnesium and sodium are retained in the bowel by sulphate or phosphate radicals and are believed to hold water in the lumen by an osmotic action. However, this is an untested hypothesis (Binder and Donowitz, 1975). Magnesium causes the release of cholecystokinin (Harvey and Read, 1973) which in turn, favours intraluminal accumulation of water and electrolytes (Moritz et al., 1973). Mag-

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nesium-containing salts should be given with caution in patients with impaired renal function since some may be absorbed (Godding, 1976).

The mechanism of action of sodium-containing saline cathartics has not been adequately studied. Sodium phosphate-biphosphate is commonly used as an enema packaged in a disposable plastic container. Sodium compounds given either orally or rectally are undesirable in sodium retention states.

1.5.2 Lactulose

The synthetic disaccharide lactulose consists of fructose and lactose which cannot be split by small intestinal or pancreatic enzymes. Such digestion is carried out by the enzymes of certain microflora, and the resulting organic acids acidify the stool (Bown et al., 1974). Although it was originally thought that lactulose enhanced the growth of lactobacilli at the expense of urea-splitting organisms, no such bacterial change has been detected (Conn and Flock, 1970). It would appear however, that the intestinal absorption of ammonia is reduced by lactulose ingestion (Elkington, 1970), hence its value in portal systemic encephalopathy.

Lactulose is effective in constipation (Wesselius-De Casparis et al., 1968), its laxative effect being due to delivery of osmotically active molecules to the colon. There is a concurrent release of gas which results in borborygmi, colic and flatulence. Severe hypernatraemia due to fluid depletion has been reported (Kaupke et al., 1977), as has superinfection with opportunistic organisms (Dubos et al., 1967). These side effects, as well as its sweet taste, its cost and its relative lack of potency, make lactulose unsuitable for the routine treatment of constipation.

2. *Rational Use of Laxatives*

The first question should not be 'which laxative should be used?' but rather, 'need one be used at all?' We have surely advanced from the days of Arbuthnot Lane who equated an empty colon with good health (Thompson, 1979). Laxatives are as important for their potential harmfulness, as they are for their value to medicine, and certainly one should avoid their long term use. Possible indications include constipation, acute illness, preparation for various diagnostic procedures, perianal disease, and special purges.

Table II. Types of constipation

1. Spastic colon type of irritable bowel
   a) With pain
   b) Without pain
2. Atonic constipation (full rectum)
3. Organic constipation (cancer, stricture, hypothyroidism, depression, drugs, etc.)

2.1 Use in Constipation

2.1.1 Types of Constipation

One must establish whether or not the patient is indeed constipated. Virtually all healthy individuals pass between 3 movements per day and 3 per week, yet some consider themselves constipated if they miss one day (Connell et al., 1965). It is important to ask patients about the consistency of their stools and the effort required to pass them. Hard, round, marble-like, difficult-to-pass stools are characteristic of the spastic colon (table II). This occurs because the sigmoid sphincter allows insufficient stool to enter the rectum and defaecation is not satisfactorily stimulated.

In atonic constipation, the stool is larger and may range from stony hard to mushy, depending on the laxative used in an effort to expel it. It goes without saying that any patient presenting with constipation, especially of recent onset, should be examined to exclude organic disease. Sigmoidoscopy should be done, followed in patients over 40 by a barium enema.

2.1.2 Which Laxative?

The individual with spastic constipation will respond to miller's bran, 1 tablespoonful 3 times a day with meals. His scybala will, over a period of days or

weeks, be transformed to softer, bulkier and more easily passed stools. However, there are several disadvantages in using bran. Bran looks and tastes like sawdust, it is difficult to mix with the diet, and awkward to use away from home. Adequate fluid intake must be ensured. It will not act on stool already in the rectum and thus it must be taken continuously to prevent, rather than cure, constipation. Patients may also notice bloating and distension early in treatment. However, if treatment is adhered to for 3 months or more they will usually notice an improvement in spastic constipation and accompanying abdominal pain.

In patients who find bran unpalatable despite a fair trial, one of the bulk laxatives (see section 1.1.2) is an acceptable alternative.

Unfortunately subjects with atonic constipation are not always responsive to treatment with bran. These individuals often have neuromuscular damage because of age, chronic debility, pseudo-obstruction or chronic laxative abuse. Bran is a safe substitute to start with, but many patients will require bowel retraining with periodic enemas and the judicious use of laxatives.

The atonically constipated person should be encouraged to develop regular bowel habits, e.g. by stationing himself at the toilet after breakfast, perhaps with a cup of coffee. He should avoid straining and, if unsuccessful, use a tap water enema on mornings when the rectum is full. If a laxative must be used, 1 or 2 tablets of bisacodyl or 'Senokot' can be given upon retiring to produce a cathartic action the following morning. Regular, futile flogging of the colon with stimulant laxatives may further damage it. If a suppository is used to trigger the defaecation reflex, a plain glycerin suppository will usually suffice. If a bisacodyl suppository is used it should be given on arising so that it acts some time after breakfast.

2.2 Use in Illness

Previously active patients subjected to enforced bedrest such as after myocardial infarction or an operation will often become constipated. This situation should be anticipated and the patient placed on bran (or another bulking agent) at the earliest possible moment. If the patient needs further treatment and can take medication orally, bisacodyl or 'Senokot' will usually suffice. Otherwise a bisacodyl suppository or a gentle tap water enema should be tried.

In the patient who becomes impacted, an oil retention enema followed by a tap water enema may be successful. None of these measures should delay manual disimpaction when it is clearly indicated. This is particularly important after gut x-rays when the rectum contains hard, barium-impregnanted stools.

2.3 Use in Preparation for Diagnostic Procedures

2.3.1 Sigmoidoscopy

Three quarters of patients undergoing sigmoidoscopy require no bowel preparation (Thompson, 1979). In the remainder, a glimpse of the colon mucosa may be obtained before appearances are altered by an enema or laxative (Meisel et al., 1977; Devroede et al., 1975). Subsequently, a disposable, hypertonic saline enema may be gently applied and the examination repeated after a bowel movement has been obtained.

2.3.2 Air Contrast Barium Enema or Colonoscopy

A clean colon is essential for air contrast barium enema or colonoscopy. This may be achieved in several ways, but the following is a good practical approach:

1. A clear fluid diet for 2 days (no milk or solid foods).
2. A laxative taken on 2 consecutive nights ('Senokot' or bisacodyl).
3. A tap water enema at bedtime the night before and on the morning of the test.

2.4 Use in Perianal Operations

The objective here is to produce as small a quantity of easily passed stool as possible. Many surgeons

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like to use dioctyl sodium sulphosuccinate postoperatively, which is said to soften the stool without greatly increasing its volume. However, it is preferable to use bran before and after the procedure to ensure that the stool is as soft and easily passed as possible. Another method, although less satisfactory, is to place the patient on a zero residue diet (clear fluids) before and after the procedure.

2.5 Use as Special Purges

From time to time it is necessary to achieve a quick purge; for example:

1. Hepatic precoma. In this condition evacuation of the colon prevents the absorption of ammonia and may allow the patient to awaken.

2. Tapeworm infestation. Tapeworms temporarily stunned by an anthelmintic drug may be shaken loose from their moorings by the administration of a purgative.

3. Treatment of poisoning. Poisons which are not retrieved from above may be flushed out below.

For these purposes, magnesium sulphate (15g) usually achieves an effective bowel movement within about 3 hours. In the case of hepatic coma, one may wish to supplement this with a tap water enema. In patients with liver failure, a saline enema is contraindicated as significant sodium absorption may occur.

3. Irrational Use of Laxatives

3.1 Long Term or Over-vigorous Use

Some patients steeped in the tradition of colon cleanliness subject their bowels to constant purgation over many years. Damage to the myenteric plexes of the colon has been demonstrated with long term use of anthracene cathartics (Smith, 1968; Rieman and Zimmerman, 1978). Such individuals develop an atonic colon, with loss of haustrations and smooth, tapering contractures termed pseudostrictures (Rawson, 1966; Thompson, 1979).

Table III. Summary of the rational use of laxatives

1. Use in constipation
   a) Spastic constipation: Miller's bran (1 tablespoonful tid with meals) is usually effective; treatment should be adhered to for 3 months or more. If bran unpalatable, a bulk laxative preparation is an acceptable alternative
   b) Atonic constipation (defaecation not triggered by a full rectum) — less satisfactorily treated with bran:
      i) Encourage development of regular bowel habits. Avoid straining
      ii) Occasional use of stimulant laxative (e.g. bisacodyl or 'Senokot') where necessary
      iii) Glycerin suppository useful to trigger defaecation reflex
2. Use during illness (e.g. postoperative period; postmyocardial infarction):
   a) Early institution of bran (or other bulking agent) is beneficial; bisacodyl and 'Senokot' should be kept in reserve
   b) If impaction occurs, an oil retention enema followed by a tap water enema may be successful (NB. manual disimpaction should not be delayed if clearly indicated)
3. Use in preparation for diagnostic procedures
   a) Sigmoidoscopy: Gentle application of a hypertonic saline enema (NB. may alter appearance of colonic mucosa)
   b) Air contrast barium enema or colonoscopy: 2-day programme of laxation required (see section 2.3.2)
4. Use in perianal operations:
   a) Use of bran before and after procedure is preferable
   b) Dioctyl sodium sulphosuccinate postoperatively said to soften stool without greatly increasing its bulk
5. Use as special purges (e.g. in hepatic precoma, expulsion of tapeworms, treatment of poisoning):
   Magnesium sulphate (15g) usually effective within 3 hours

Vigorous purgation may produce a paradoxical diarrhoea complicated by water and sodium depletion (Fortran and Ingelfinger, 1968). Since renin and aldosterone are released, hypokalaemia may result (Cummings et al., 1974). Malabsorption and a protein-losing gastroenteropathy have also been described in association with ritual purgation (French et al., 1956; Heizer et al., 1968). One patient had clubbing of the fingers which disappeared when senna

was withdrawn, and reappeared when the drug was started again (Silk et al., 1975).

It is curious that some patients, even with copious diarrhoea, will conceal their laxative use from the clinician. They may complain simply of diarrhoea or of alleged constipation, weakness, aches and pains, and may have an obvious emotional disorder. In this situation, the diagnosis can only be made by searching the patient's medicine drawer for the offending drug or by examining the urine for phenolphthalein and anthraquinone derivatives (French et al., 1956; Cummings et al., 1974; Silk et al., 1975). Another clue to the chronic use of anthracene glycosides is the presence in the colonic mucosa of a brownish stain known as melanosis coli (Thompson, 1979). However, some patients, even when faced with incontrovertible evidence of laxative abuse, may deny it or simply continue to take the laxative.

3.2 Routine Purgation of Ill Patients

Fortunately, vigorous routine purgation of ill patients has become less popular than it used to be (Witts, 1937). Unnecessary purgation in patients with already precarious hydration and electrolyte balance is clearly irrational.

3.3 Use of Potentially Hazardous Preparations

There are a number of dangerous purgatives still available. Mineral oil and oxyphenisatin have already been discussed (section 1.3.1). The ancient remedy, mercurous chloride, is — believe it or not — still in use, and was the cause of two recent poisonings (Wands et al., 1974).

The cathartic qualities of oral bile salts are well known (Mekhjian et al., 1971), and preparations containing these naturally occurring substances are still readily available at some pharmacies. However, bile salts have adverse effects on the upper gastrointestinal tract, and should not be recommended.

Table IV. Irrational use of laxatives

1. Long term administration of stimulant cathartics: Can lead to an atonic colon in which neuromuscular apparatus is permanently damaged (NB. such use may be denied by patient)
2. Over-vigorous purgation: May produce a paradoxical diarrhoea complicated by electrolyte derangement (hyponatraemia and hypokalaemia), malabsorption and protein-losing enteropathy
3. Routine purgation of ill patients (unnecessary)
4. Use of potentially hazardous preparations: Mineral oil (liquid paraffin), oxyphenisatin, bile salts, soap enemas should be avoided

As well as damaging the intestinal mucosa, the traditional soapsuds enema may deliver large amounts of potassium or sodium which may cause hypovolaemic shock (Pike et al., 1971) and hyperkalaemia (Young et al., 1968). Even the commonly used sodium phosphate-biphosphate enemas may result in mucosal damage (Meisel et al., 1977), perforation of the rectum (Turrell, 1960), and hypocalcaemic tetany (McConnell, 1971).

As with any other drug, the indications for the use of a laxative should be clear, and its potential side effects fully appreciated.

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